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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/690,199 | 10/21/2003 | Igor Astsaturov | API-02-13-US | 3672 |

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| EXAMINER | |
|---|---|
| SHEN, WU CHENG WINSTON | |

| ART UNIT | PAPER NUMBER |
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| 1632 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/690,199 | ASTSATUROV ET AL. | |
| | Examiner | Art Unit | |
| | Wu-Cheng Winston Shen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response to the Non-Final office action mailed on 07/25/2006 has been received and entered. In the response filed on 01/25/2007 by applicant, no amendment to the claims is filed in the response.

This application 10/690,199 filed on Oct. 21, 2003 claims benefit of provisional application 60/420,425 filed on Oct. 22, 2002. The publication number of this application 10/690,199 is US 2004/0223949 A1, published on Nov. 11, 2004.

Claim 2 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

This application contains claims 1, 5, 6, 11, and 12 drawn to an invention nonelected with traverse in Paper No. filed on 5/15/2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

***Status of claims:*** Claims 1 and 3-22 are currently under examination

### *Objections to Specification*

1. Previous objection to the spacing between words of the lines of the specification, line 19, page 20 and line 10, page 30, which makes reading difficult, is ***withdrawn*** because the extra long space between words on the originally filed specification has been fixed in the publication of instant application, US 2004/0223949 A1.

### *Claim Objections*

2. Claims 1, 5, 6, 11, and 12 are objected for recitation of non-elected inventions as Applicant responded on 5/15/2006 to the Requirement of Restriction/Election mailed on 03/13/2006. Specifically, Applicant elected nucleic acid encoding a tumor antigen (for claim 1). Claim 1 encompasses protein therapy, which is non-elected subject matter.

### *Claim Rejection – 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Previous scope of enablement rejection of claims 1, and 3-22 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating melanoma in a host by direct administration to the tumor a polynucleotide encoding a tumor antigen followed by administration of a cytokine wherein said administrating of the polynucleotide and cytokine result in an increased T cell response in the host relative to the T cell response that occurs following administrating of the polynucleotide alone, does not reasonably provide enablement for treating any cancer wherein a polynucleotide encoding a tumor antigen is administrated by any route followed by administration of a cytokine, is ***maintained*** for the reasons of record advanced on pages 4-9 of the office action mailed on 07/25/06.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to perform the invention commensurate in scope with these claims.

***Applicant's Arguments***

With respect to the aspect of the rejection regarding the breadth of the claims relating to treatment of any type of cancer, Applicant argues that claim 1 requires administration of a nucleic acid encoding a tumor antigen such that the host develops an immune response thereto. Selection of the tumor antigen is a key determinant for each particular type of cancer; the process of selecting a tumor antigen would not place an undue burden upon the skilled artisan. In fact, the specification provides list of exemplary tumor antigens (i.e., paragraph 0018 of US 2004/0223949A 1). As described therein, each of these tumor antigens is known by those of skill in the art to be associated with at least one particular type of cancer. For instance, it is known that gpl00 and the MAGE genes are expressed in melanoma, CEA is expressed in certain colorectal tumors, and PSA is expressed in prostate cancers. It is certainly within the skill set of the highly-trained scientists involved in this field to select a tumor antigen, and therefore a type of cancer, in which to apply the claimed method. Accordingly, Applicants believe the claimed method is enabled with respect to the application thereof to "any cancer" (see paragraph bridging pages 2-3 of Applicant's Remarks dated 01/25/2007).

With respect to the use of "any route", the Examiner alleged on p. 5 of the Office Action that "[t]he choice of a particular route of administration suitable for treatment of one type of cancer may not be applicable to the treatments of other cancers." However, Applicant argues the claimed invention is not dependent upon a particular route of administration (i.e., direct

administration to a particular site). It is the combination of the administration of a nucleic acid encoding a tumor antigen and the subsequent administration of a high dose of cytokine that is inventive. All that is required in part (a) of claim 1 is that a nucleic acid encoding a tumor antigen is administered such that the host develops an immune response to the tumor antigen. As stated in the specification, many suitable routes of administration are in fact available to one of skill in the art. Even if it were true that a particular route of administration suitable for one type of cancer was not suitable to every other type of cancer, it would not be an undue burden for the skilled artisan to select another route suitable to that other type of cancer. As suggested in Applicants' specification and the articles cited by the Examiner, many such routes are known in the art.

With respect to the aspect of the rejection regarding the breadth of the claims relating to treatment by administration of a polynucleotide and/or a cytokine via any route, Applicant argues, in addition, the successful administration of tumor antigens to human beings by several different routes (i.e., intradermal, subcutaneous, intranodal, and intravenous) has been shown by, for example, Marshall, et al. (J. Clin. Oncol. 18(23): 3964-3973 (2000), van der Burg, et al. (Clin. Cancer Res., 8:1019-1027 (2002), Astatsturov, et al. (the Applicants; Clin. Cancer Res. 9:4347-4355 (2003), Karakinas, et al. (J. Immunol. 171: 4898-4904 (2003), van Baren, et al. (J. Clin. Oncol. 23 (35): 9008-9021 (2005). Thus, the skilled artisan would have many routes to choose from in practicing the claimed invention.

The Examiner further alleged that the instant claims are not enabled as to "any cytokine". Applicants respectfully disagree (see page 3 of Applicant Remarks dated 01/25/2007). The specification provides a list of potentially useful cytokines at paragraphs 0044 and 0045 (US

2004/0223949A1). Many others are known in the art. *The suitability of any particular cytokine to any particular type of cancer may involve some experimentation, but Applicants do not believe such experimentation would be undue.*

Applicants were the first to coordinate the use of a nucleic acid encoding a tumor antigen and high doses of cytokine(s) to produce an anti-tumor immune response. *With Applicants' description of the method in hand, the burden placed upon the skilled artisan in identifying and selecting particular components to use therein would not be undue.* Accordingly, Applicants believe the claimed invention is enabled and respectfully request that this rejection be withdrawn.

***Response to Applicant's Arguments***

Applicant's arguments filed 01/25/2007 have been fully considered but they are not persuasive because of the reasons discussed below.

The following statements are recited from applicant's arguments against the rejection of claims 1, 9-10, and 16-22 under 35 U.S.C. 103(a) as being unpatentable over Paoletti (U.S. patent number 5,942,235; issued on August 24, 1999) in view of Kirkwood et al. (Kirkwood et al. *J Clin Oncol.* 19(9): 2370-80, 2001): "*In addition, and in contrast to the Examiner's allegations, Applicants do not believe the skilled artisan would have had a reasonable expectation of success in practicing the claimed invention until the method was actually carried out and the results thereof observed. There was no reason to believe that administration of high-dose cytokine following the initial immune response resulting from administration of the nucleic acid encoding the tumor antigen would result in the clinical results observed by the Applicants*". Accordingly, applicants essentially agree with the Examiner's conclusion that the claimed

invention of instant application is not fully enabled and lacks of predictability of reasonable expectation of success unless the method was actually carried out and the results thereof observed documenting various combinations of any tumor antigen and any cytokine in treating any cancer by claimed method.

Therefore, the claimed method administering a given nucleic acid encoding a given tumor antigen administered by a given route with a given combination of asserted "high dose" cytokine needs to be evaluated on a case-by-case basis for treating cancer via asserted enhanced T-cell response. In this regard, it is noted that in the Example 2 of instant application, which documented toxicity in the treatment of melanoma using high-dose INF-α and a recombinant viral vector in all 7 patients enrolled in the trial and the incidence rate of toxicity based on applicant's claimed method of treatment (100%) is three folds higher than what reported by other trial (33%). Consequently, dose reductions and treatment delays due to toxicity are needed.

The Examiner notes that the specification does not disclose any information regarding the effect of enhanced T cell response as a result of variation in the timing of administering a high dose of a cytokine to the host cell following administration of a nucleic acid encoding a tumor antigen. *Subsequent* administration of cytokine is the only limitation recited in the claim, which is considered as the novelty of instant application. The specification fails to provide enabling support in this regard.

The Examiner also acknowledges that applicant attached to the response filed on 01/25/ 2007 with 11 more publications, among which most of them are post-filing arts with four references published in 2007. The applicant does not discuss why these references provide enabling support for the claimed invention. Based on the title and abstract, the only relevant

reference addressing claimed novelty of instant application (i.e. subsequent administration of high dose cytokine) is the publication by Astsaturov et al., 2003 (the first inventor of instant application) published on 10/01/2003, which is between claimed priority date 10/22/2002 and the filing date 10/21/2003 of instant application. The content of Astsaturov et al., 2003 is essentially the same as disclosed in the Example 2 of instant application.

In conclusion, the Examiner acknowledges that the specification of instant application discloses sufficient information for "proof of concept" at the time of filing and is enabled to a certain scope, as recited in the rejection under 35 USC 112 first paragraph, which is encompassed by the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. Claims 1, and 3-17 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Previous rejection is ***maintained*** for the reasons of record advanced on page 9 of the office action mailed on 7/25/06

***. Applicant's Arguments***

As indicated by the specification, the term "high dose" is not tied to any particular amount of cytokine. The meaning of the term "high dose", in its most basic form, is a dose above what is commonly known to be a low dose. While the exact amount of cytokine falling within the meaning of "high dose" may not be entirely consistent within the art, ranges corresponding thereto are art-recognized for several cytokines. It is understood that such ranges

vary depending on the particular cytokine. The specification describes the parameters of treatment with high dose interferon (paragraph 0072 of US 24223949A1; Kirkwood, et al. J. Clin. Oncol. 14:7-17 (1996) and J. Clin. Oncol., 18(12): 2444-2458 (2000)). The meaning of a "high dose" of IL-2 is art-recognized (see, for example, Lindsey, et al. J. Clin. Oncol. 18(9): 1954-1959 (2000); Phan, et al. J. Clin. Oncol. 19(15): 3477-3482 (2001); McDermott, et al. J. Clin. Oncol. 23(1): 133-141 (2005)). Similar information for determining the nature of a high dose is available for other cytokines including, for example, GM-CSF (Abramovich, et al. Abstract No. 205 of 1999 ASCO Meeting), IL-11 (Kurzrock et al. J. Clin. Oncol. 19(21): 4165-4172 (2001)), and TNF-alpha (Rossi, et al. Ann. Surg. Oncol. 11(2): 173-177 (2004)). Applicants do not believe this phrase would be unclear to one of skill in the art. As such, withdrawal of this rejection is respectfully requested.

***Response to Applicant's Arguments***

Applicant's arguments filed 01/25/2007 have been fully considered but they are not persuasive because of the reasons discussed below.

The examples cited by Applicants clearly indicate that the definition of "high dose of cytokine" varies from one cytokine to another and is determined on a case-by-case basis. The specification fails to provide any specific guidance regarding how one skilled person in the art can extrapolate the amount of "high dose of cytokine" from one specific cytokine to another cytokine.

This is especially important in light of the Example 2 of instant application, which documented toxicity in the treatment of melanoma using high-dose INF-$\alpha$ and a recombinant viral vector for treatment in all 7 patients enrolled in the trial and the incidence rate of toxicity

based on Applicant's claimed method of treatment (100%) is three folds higher than what reported by other trial (33%). Consequently, dose reduction and treatment delays due to toxicity are needed. Therefore, in the absence of any guidance and/or operational definition of "high dose of cytokine", the term is considered as vague and indefinite as part of a critical step of the claimed method.

***Claim Rejection – 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Previous rejection of claims 1, 3-8, 14-15 under 35 U.S.C. 102(b) as being anticipated by Paoletti, 1999 (U.S. patent number 5,942,235; issued on August 24, 1999), is ***maintained*** for the reasons of record advanced on pages 10-11 of the Non-Final office action mailed on 07/25/06.

The followings are the recitation of the pages 10-11 of the Non-Final office action mailed on 07/25/06.

With regard to claims 1 and 3, Paoletti teaches attenuated recombinant viruses containing DNA coding for a cytokine and/or a tumor associated antigen (TAA), as well as methods and compositions employing the viruses for cancer therapy (See abstract). Paoletti also teaches that immune responses in a mammalian host against tumor cells are mediated by T-cells, particularly cytotoxic T lymphocytes (CTLs); white blood cells capable of killing tumor cells and virus-infected cells (column 7, lines 55-57). Furthermore, Paoletti teaches the administration of a

cytokine secreted from modified tumor cells can subsequently be utilized for active immunization. The therapeutic potential for such an administration is based on the ability of cytokines to alter the presentation of TAAs to achieve systematic anti-tumor activity (See column 16, lines 3-8).

With regard to claims 4-8 and 14-15, Paoletti teaches (1) viral vectors including poxvirus, vaccinia virus, and avipox virus (See, for instances, column 2, background of the invention, second paragraph; claims 1-8); NYVAC, ALVAC, and TROVAC based recombinant viruses expressing TAAs plus or minus specific cytokines for adoptive immunotherapy (See column 15, lines 45-48, column 17, lines 8-9); as well as canarypox virus (column 16, line 55) and fowlpox virus (column 16, line 64); (2) expression of tumor antigens --- CEA, carcinoembryonic antigen, (columns 70-77, example 17); p53 (columns 65-68, example 15); MAGE-1 (columns 68-70, example 16); and cytokines --- human INFγ (columns 83-84, example 21), IL-2 (column 79-80, example 19) in both ALVAC and NYVAC based viral vectors.

Thus Paoletti, 1999 clearly anticipates claims 1, 3-8, 14-15 of instant application.

***Applicant's Arguments***

Applicant's arguments focused on the limitation "subsequently administering to the host a high dose of a cytokine" recited in claim 1 of instant application, which applicant argued that Paoletti, 1999 did not teach this limitation.

***Response to Applicant's Arguments***

As stated in the rejection that Paoletti 1999 teaches *the administration of a cytokine secreted from modified tumor cells can subsequently be utilized for active immunization.* The

therapeutic potential for such an administration is based on *the ability of cytokines to alter the presentation of TAAs to achieve systematic anti-tumor activity* (See column 16, lines 3-8).

Bearing broad and reasonable interpretation in mind, the statement "cytokine secreted from modified tumor cells can subsequently be utilized for active immunization" disclosed by Paoletti 1999 reads on the limitation "subsequently administering to the host a high dose of a cytokine" recited in claim 1 of instant application because the statement by Paoletti 1999 encompass administering cytokine before and/or after the administration of a viral vector expressing a tumor antigen. Supporting this interpretation, Paoletti 1999 also discloses that the expression of specific cytokines or the co-expression of specific cytokines with TAAs by NYVAC-, ALVAC-, and TROVAC-based recombinant viruses can enhance the numbers and anti-tumor activities of CTLs associated with tumor cell depletion or elimination (See lines 29-31, column 14, Paoletti 1999), which clearly indicates that the administration of cytokine secreted by a tumor cell taught by Paoletti 1999 is distinct from co-expression of a tumor antigen and a cytokine from a viral vector.

***Claim Rejection – 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Previous rejection of claims 1, 9-10, and 16-22 under 35 U.S.C. 103(a) as being unpatentable over Paoletti (U.S. patent number 5,942,235; issued on August 24, 1999) in view of Kirkwood et al. (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 19(9): 2370-80, 2001), is ***withdrawn*** because applicant's arguments were found persuasive regarding lack of predictability to assure a reasonable expectation of successful in practicing the claimed invention until the method was actually carried out and the results thereof observed.

7. Previous rejection of claims 1, 3-7 and 11-13 under 35 U.S.C. 103(a) as being unpatentable over Paoletti (U.S. patent number 5,942,235; issued on August 24, 1999) in view of Schlom et al. (U. S. patent number 6,045,802, issued on April 4, 2000), is ***withdrawn*** because applicant's arguments were found persuasive regarding lack of predictability to assure a reasonable expectation of successful in practicing the claimed invention until the method was actually carried out and the results thereof observed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Conclusion***

9. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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